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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
MARVICH, MARIA	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 08/11/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/049,502	SEBTI, SAID M.	
	Examiner	Art Unit	
	Maria B Marvich, PhD	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 July 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16* is/are pending in the application.

4a) Of the above claim(s) *6 and 13-15* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,7-12 and 16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *15 February 2002* is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *6/7/02, 11/4/02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This office action is in response to a response to a restriction requirement filed 7/6/04. Claims 1-16 are pending in the application.

Election/Restrictions

Applicant's election without traverse of Group I (claims 1-5, 7-12 and 16) in the amendment filed 7/7/04 is acknowledged. Therefore, claims 6 and 13-15 have been withdrawn as drawn to non-elected subject matter and claims 1-5, 7-12 and 16 are under examination herein.

Information Disclosure Statement

Information Disclosure Statements filed 6/7/02 and 11/4/02 have been identified and the documents considered. The signed and initialed PTO Form 1449s has been mailed with this action.

Priority

Applicants indicate the filing date of this application as 2/13/02. This contradicts the filing date listed in PALM and accorded by the 371 Acceptance Letter which lists the filing date as 2/15/02 based upon completion of 371 (c)(1), (c)(2) and (c)(4) requirements.

Claim Rejections - 35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 5 is vague and indefinite in that the metes and bounds of "cell comprises a solid tumor" are unclear. It is unclear how a tumor can be a component of a cell as a tumor is comprised of multiple cells.

Claim Rejections - 35 USC § 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-5, 8-12 and 16 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicants recite a genus of RhoB variant proteins.

Applicants recite a broad genus of oncogenic signaling pathways that are inhibited by RhoB.

The written description requirement for genus claims may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant identifying characteristics,

i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with known or disclosed correlations between function and structure, or by a combination of such characteristics sufficient to show that the applicant was in possession of the claimed genus.

Applicants recite methods of inhibiting growth of a cancerous cell, suppression of malignant transformation, inhibition of tumor growth, induction of apoptosis in a transformed cell, inhibition of oncogenic signaling, prevention of malignant transformation and decreasing protein phosphorylation in a transformed cell by contacting a cell interior with RhoB or variants thereof. Applicant teach that RhoB protein or variants thereof denotes RhoB-F, RhoB-GG and RhoB-WT proteins and variants thereof that may be derived from these proteins. Furthermore, variants are said to possess at least one characteristic biological activity of RhoB for example truncations, oxidations, amino acid substitutions, post-translation modifications, labeling or linkage to another molecule (page 6, line 7-12). While the instant disclosure teaches that RhoB-WT and RhoB-F and RhoB-GG induce apoptosis, inhibit Erk2 and Akt phosphorylation and suppress transformation, applicants do not disclose the structures of these proteins or the structural regions required to provide at least one function of RhoB. RhoB-F and RhoB-GG are described as mutants that can be farnesylated (F) or geranylgeranlyated (GG). By applicants' definition, RhoB-F and RhoB-GG may be variants based upon their post translation modifications. However, the specification is not clear as to whether RhoB-F and RhoB-GG are examples of variants or not. Given the diversity of RhoB variants and the inability to determine which will also possess the biologically active form, it is concluded that the invention must be empirically determined. In an unpredictable art, the

disclosure of one species would not represent to the skilled artisan a representative number of species sufficient to show applicants were in possession of claimed genus.

The disclosure demonstrates that RhoB inhibits phosphorylation of proteins of two signaling pathways. The first pathway is the growth factor stimulated PI3 kinase/Akt pathway in which phosphorylation of the serine threonine kinase Akt is inhibited 50% by RhoB. The second pathway is the growth factor stimulated Erk1/Erk2 pathway in which phosphorylation of Erk2 is inhibited by about 70%. While applicants recite that Erk1 phosphorylation is inhibited, it is difficult to discern this from the disclosure (see Figure 3 and page 16, line 15-23). Erk2 and Akt are components of oncogenic signaling pathways that must be activated by phosphorylation and be inhibited by RhoB. The disclosure of these two signaling proteins is not accompanied by a disclosure as to their relative properties such that any signaling pathway that is inhibited by RhoB can be identified. There is no actual reduction to practice or clear description of what is required of the oncogenic signaling pathway such that those regulated by RhoB can be identified. Given the diversity of proteins and the inability to determine which are oncogenic singalling proteins and which RhoB will also inhibit, it is concluded that the invention must be empirically determined. In an unpredictable art, the disclosure of two species would not represent to the skilled artisan a representative number of species sufficient to show applicants were in possession of claimed genus.

Claims 1-5, 7-12 and 16 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for *in vitro* contacting of the interior of a cell with RhoB protein to suppress growth and malignant transformation of a cell,

suppress tumor growth, induce apoptosis and decrease phosphorylation of Akt and Erk2 does not reasonably provide enablement for *in vivo* contacting of a cell with RhoB protein or variants for the aforementioned processes or for combination therapy with RhoB and at lest one additional therapy. Furthermore, the specification does not reasonably provide enablement for preventing malignant transformation. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the patent coupled with information known in the art without undue experimentation (*United States v. Telectronics, Inc.*, 8 USPQ2d 1217 (Fed. Cir. 1988)). Whether undue experimentation is required is not based on a single factor but is rather a conclusion reached by weighing many factors (See *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Inter, 1986) and In *re Wands*, 8USPQ2d 1400 (Fed. Cir. 1988); these factors include the following:

1) **Nature of invention**. The invention is directed to methods of cancer or oncogenic therapy using RhoB or variants thereof. The invention utilizes disciplines of molecular biology, cell biology and clinical technology.

2) **Scope of the invention**. The claims specifically recite methods of inhibiting growth of a cancerous cell, suppression of malignant transformation, inhibition of tumor growth, induction of apoptosis in a transformed cell, inhibition of oncogenic signaling, prevention of malignant transformation, decreasing phosphorylated protein in a transformed cell and inhibiting cell growth in combination with one additional therapy.

Each of these goals are met by the step of administering RhoB to the cell. Applicants disclose that a use of these methods is in gene therapy which exacerbates the lack of guidance associated with meeting the goals of such varied methods. Furthermore, applicants recite that malignant transformation is inhibited. Prevention of any disease is an unpredictable art..

3) **Number of working examples and guidance**. Panc-1 and A549 cell cultures were transfected with constructs expressing RhoB, RhoB-F and RhoB-GG. Cells expressing these constructs exhibited reduced foci formation and little growth in soft agar. Hence RhoB was accorded a role in antagonizing tumor growth and malignant transformation. The transfected cells exhibited enhanced apoptosis and decreased phosphorylation of Akt and Erk2. Foci formation was also decreased in C-33A, Hela and Saos-2 cells transfected with RhoB. Applicants then demonstrated that Panc-1 cells expressing RhoB exhibited suppressed tumor growth in nude mice. Based upon these observations, applicants recite a variety of therapeutic approaches based upon administration of RhoB to a cell to inhibit cancer cell growth, transformation, apoptosis, tumor growth, oncogenic signaling, protein phosphorylation and in combination with an additional therapy inhibition of cancer cell growth.

Guidance for *in vivo* administration of RhoB is broad and general except to describe use of recombinant viral vectors such as retroviruses are used as a delivery vehicle of RhoB nucleic acids. The guidance is more a general review of the art related to *in vivo* methods. Applicants' disclosure lacks any guidance at al for the method of combining RhoB therapy with an additional therapy such as chemotherapy or radiotherapy.

4) **State of Art**. The instant invention recites that RhoB can contact the interior of the cell following administration of either nucleic acid encoding RhoB or RhoB protein. Administration of nucleic acids utilizes the art of gene therapy which is a highly unpredictable art. Three major obstacles for gene therapy are 1) gene expression 2) gene delivery and 3) efficacy and toxicity of administration (Meng and El-Deiry, 1999). Vector based and non-vector based means of introducing the DNA into the cell to be expressed have not successfully overcome any of these obstacles. The route of delivery itself presents an obstacle to be overcome for the application of the vector therapeutically. Verma and Somia (1997) teach, "The Achilles heel of gene therapy is gene delivery... the problem has been an inability to deliver genes efficiently and to obtain sustained expression". No modes of gene administration were proposed in the specification including means and routes of administration except to generally refer to gene expression vectors and retrovirus. To date, no single mode of gene transfer has provided a viable option for successful gene therapy protocols. As noted by Marshall, (Marshall et al., Science January 17, 2003) one of the main issues in using retroviral vectors for gene therapy is determining how to use the vector in vivo without causing leukemia or other cancers in the patients being treated. This is not merely a safety issue for FDA concern but is a fundamental issue underlying how the skilled artisan can make and **use** the claimed invention for the recited treatments.

The art of protein therapy also is highly unpredictable. Torchilin and Lukyanov (2003) teach that there are many unresolved problems concerning the delivery of proteins and peptides such as rapid elimination from the circulation through renal filtration ,

enzymatic degradation, uptake by the reticuloendothelial system and accumulation in non-targeted organs and tissues and inefficient cell entry (see Box 1, page 260).

5) **Unpredictability of the art**. The unpredictable nature of administration of RhoB nucleic acid or protein *in vivo* is exacerbated due to the lack of recited methods. Many parameters must be addressed for *in vivo* gene or protein delivery such as lack of toxicity to normal tissues, and the effect of the immune response as well as doses to be administered, dose schedules etc. For example, what level of expression or protein is necessary to achieve therapeutic affects without toxicity to normal cells that results from leaky expression of the viral gene required for replication?

Applicants demonstrate a potential role for RhoB in multiple processes such as malignant transformation and apoptosis and even tumor growth in nude mice. However, historically *in vitro* and animal models have not correlated well with *in vivo* clinical trial results in patients. It is not clear that reliance on experimental models accurately reflects the relative superiority or efficacy of the claimed therapeutic strategy and applicants present no disclosed or art recognized nexus between the xenograft and nude mice experimental models and the human disease state. "Although animal studies have suggested low toxicity and excellent efficacy, these investigation have been limited by the use of immuno-deficient mice" (Meng and Deiry, p. 6, column 1). The success of any *in vitro* assays or *in vivo* animal models cannot be considered as evidence of success of treatment, *in vitro* results rarely correlate well with *in vivo* clinical trial results in patients and have not translated into successful human therapies. Many *in vitro* and animal models that are provided as evidence of success of treatment have not translated into successful treatment in humans.

Applicants recite a method of preventing malignant transformation. The process of preventing disease is highly unpredictable. In humans, the claimed diseases are usually established before therapy is offered. The specification does not adequately teach how to effectively predict for whom prevention would be required. The lack of well defined targets (i.e. for whom the disease is prevented) compounded by the lack of disclosure for treatment with RhoB makes it unpredictable as how to determine patients most likely to benefit from treatment, how to deliver to multiple targets, when to deliver, how to keep the drug in place long enough to achieve full activity and how to overcome the potential deleterious effects of inhibition of wound healing.

6) **Summary**. The invention recites a single method step for of inhibiting growth of a cancerous cell, suppression of malignant transformation, inhibition of tumor growth, induction of apoptosis in a transformed cell, inhibition of oncogenic signaling, prevention of malignant transformation and decreasing phosphorylation of protein in a transformed cell. The unpredictability of using the claimed invention in therapy is accentuated due to the lack of methods or processes disclosed in the instant specification that exacerbates a highly unpredictable art.

In view of predictability of the art to which the invention pertains and the lack of: undue experimentation would be required to practice the claimed methods with reasonable expectation of success, absent a specific and detailed description in the specification. Given the above analysis of the factors which the courts have determined are critical in determining whether a claimed invention is enabled, it must be concluded that the skilled artisan would have had to have conducted undue unpredictable experimentation in order to practice the claimed invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 1-2, 5 and 7-11 are rejected under 35 U.S.C. 102(a) as being anticipated by Chen et al (JBC, 2000, Vol 275(24) pages 17974-17978; see entire document).

This rejection is based upon a reading of the claims based upon administration of RhoB *in vitro* to cells. As stated above in the 112, first paragraph rejection, "the success of any *in vitro* assays or *in vivo* animal models cannot be considered as evidence of success of treatment, *in vitro* results rarely correlate well with *in vivo* clinical trial results inpatients and have not translated into successful human therapies". Hence this rejection cannot be considered to provide an enabling disclosure for *in vivo* therapy as recited in the instant application.

Chen et al teach that Panc-1, C-33A, HeLa and Saos-2 cell cultures were transfected with constructs expressing RhoB, RhoB-F and RhoB-GG. Cells expressing these constructs exhibited reduced foci formation. Panc-1 cells transfected with these constructs induce apoptosis and little growth in soft agar. The transfected cells exhibited enhanced apoptosis and decreased phosphorylation of Akt, Erk1 and Erk. Applicants then demonstrated that Panc-1 cells expressing RhoB exhibited suppressed tumor growth in nude mice.

Conclusion

No claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maria B Marvich, PhD whose telephone number is (571)-272-0774. The examiner can normally be reached on M-F (6:30-3:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, PhD can be reached on (571)-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Maria B Marvich, PhD
Examiner
Art Unit 1636

August 5, 2004

GERRY LEFFERS
PRIMARY EXAMINER